CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2

International Chemical Identification:

3-methylpyrazole

EC Number: **215-925-7**

CAS Number: **1453-58-3**

Index Number: **NA**

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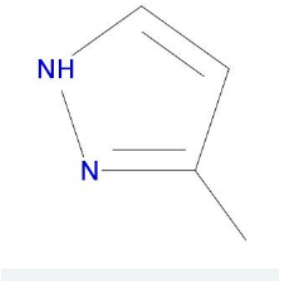
CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	3-methyl-1H-pyrazole
Other names (usual name, trade name, abbreviation)	3-methylpyrazole
ISO common name (if available and appropriate)	
EC number (if available and appropriate)	215-925-7
EC name (if available and appropriate)	3-methylpyrazole
CAS number (if available)	1453-58-3
Other identity code (if available)	
Molecular formula	C4H6N2
Structural formula	
SMILES notation (if available)	
Molecular weight or molecular weight range	82.10
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	
Description of the manufacturing process and identity of the source (for UVCB	

substances only)	
Degree of purity (%) (if relevant for the entry in Annex VI)	>98.2%

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self- classification and labelling (CLP)**
3-methylpyrazole EC n° 215-925-7	>98.2 - <98.6%	NA	Acute Tox. 4, H302 Skin Corr. 1B, H314 Eye Dam. 1, H318 Repr. 2, H361

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self- classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**
See confidential annex				The impurities are not considered relevant for the classification of the substance

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	**Function**	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The additive contributes to the classification and labelling**
NA					

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATEs	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	3-methylpyrazole	215-925-7	1453-58-3	Repr.1B Acute Tox. 4 STOT RE 1 Skin Corr. 1B Eye Dam. 1	H360D H302 H372 (lung) H314 H318	GHS08 GHS07 GHS05 Dgr	H360D H302 H372 (lung) H314 H318		oral: ATE = 500 mg/kg bw	
Resulting Annex VI entry if agreed by RAC and COM	TBD	3-methylpyrazole	215-925-7	1453-58-3	Repr.1B Acute Tox. 4 STOT RE 1 Skin Corr. 1B Eye Dam. 1	H360D H302 H372 (lung) H314 H318	GHS08 GHS07 GHS05 Dgr	H360D H302 H372 (lung) H314 H318		oral: ATE = 500 mg/kg bw	

Table 6: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	hazard class not assessed in this dossier	No
Oxidising gases	hazard class not assessed in this dossier	No
Gases under pressure	hazard class not assessed in this dossier	No
Flammable liquids	hazard class not assessed in this dossier	No
Flammable solids	hazard class not assessed in this dossier	No
Self-reactive substances	hazard class not assessed in this dossier	No
Pyrophoric liquids	hazard class not assessed in this dossier	No
Pyrophoric solids	hazard class not assessed in this dossier	No
Self-heating substances	hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	hazard class not assessed in this dossier	No
Oxidising liquids	hazard class not assessed in this dossier	No
Oxidising solids	hazard class not assessed in this dossier	No
Organic peroxides	hazard class not assessed in this dossier	No
Corrosive to metals	hazard class not assessed in this dossier	No
Acute toxicity via oral route	Acute Tox. 4, H302	Yes
Acute toxicity via dermal route	data lacking	No
Acute toxicity via inhalation route	data conclusive but not sufficient for classification	Yes
Skin corrosion/irritation	Skin Corr. 1B, H314	Yes
Serious eye damage/eye irritation	Eye Dam. 1, H318	Yes
Respiratory sensitisation	hazard class not assessed in this dossier	No
Skin sensitisation	hazard class not assessed in this dossier	No
Germ cell mutagenicity	hazard class not assessed in this dossier	No
Carcinogenicity	hazard class not assessed in this dossier	No
Reproductive toxicity	Repro. 1B, H360D	Yes
Specific target organ toxicity-single exposure	hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	STOT RE 1, H372	Yes
Aspiration hazard	hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	hazard class not assessed in this dossier	No
Hazardous to the ozone layer	hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

3-methylpyrazole is a chemical substance which is registered under REACH (1907/2006/EC). The substance is not listed in annex VI of CLP and classification and labelling was not previously discussed by the TC C&L The substance is self-classified in the public registration dossier as :

Acute Tox. 4, H302
Skin Corr. 1B, H314
Eye Dam. 1, H318
Repr. 2, H361

The substance is also under substance evaluation (REACH).

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

[A.] There is no requirement for justification that action is needed at Community level : the substance is toxic to reproduction. The substance is self-classified as Repr. 2, H361.

[B.] Justification that action is needed at Community level is required.

Justification for the hazard classes/differentiations other than reproductive toxicity and within the scope of this public consultation :

- Disagreement by DS with current self-classificationt (by the notifiers and/or registrants)
- Requirement for harmonised classification by other legislation or process : relevant for f.i. substance evaluation

5 IDENTIFIED USES

The substance is used in fertilisers.

6 DATA SOURCES

Registration dossier

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Liquid at 20°C and 101.3 kPa	Anonymous 1 (2011)	EPA OPPTS 830.6303 GLP Rel.1
Melting/freezing point	> -53.9 - < -39.1 °C at 1 013 hPa	Anonymous 1 (2011)	OECD TG 102 (capillary method) GLP Rel.1 3-methylpyrazole showed a melting range, no melting point
Boiling point	204 °C at 1 013 hPa	-W.M. Haynes, 2011 CRC-Handbook of Chemistry and	No guideline available GLP : not specified Rel.2

Property	Value	Reference	Comment (e.g. measured or estimated)
		Physics, 91 st Edition, 2011, p. 3-372 -Syracuse Research Corporation (SRC), Physical Properties Database (PHYSPROP), 2012	
Relative density	1.02 g/cm³ at 25°C	W.M. Haynes, 2011 CRC-Handbook of Chemistry and Physics, 91 st Edition, 2011, p. 3-372	No guideline available GLP : not specified Rel.2
Vapour pressure	182 Pa at 20 °C and 243 Pa at 25°C	Anonymous 2 (2009)	OECD TG 104 (static method) GLP Rel.1
Surface tension	63.26 mN/m at 20°C	Anonymous 3 (2009)	OECD TG 115 (plate method) GLP Rel.1
Water solubility	> 1 000 g/L at 20°C	Anonymous 4 (2011)	OECD TG 105 (flask method) Rel.1 Deviation from guideline : Due to the high water solubility of the substance, it was not possible to weigh the fivefold saturation concentration of the test item in water in order to perform a main study
Partition coefficient n-octanol/water	Log Pow= 0.475 at 25°C, pH6.9	Anonymous 5 (2008)	OECD TG 117 (HPLC method) GLP Rel.1
Flash point	103.5 °C at 1 013 hPa	Anonymous 6 (2011)	EU A.9 (equilibrium method closed cup) GLP Rel. 1
Flammability	Non-flammable		
Explosive properties	Non explosive	Anonymous 7 (2008)	EU A.14 GLP Rel.1
Self-ignition temperature	532 °C at 1 013 hPa	Anonymous 8 (2011)	EU A.15 GLP Rel.1
Oxidising properties	Based on the molecular structure, 3-methylpyrazole is considered non oxidising		

Property	Value	Reference	Comment (e.g. measured or estimated)
Granulometry	Not relevant for a liquid		
Stability in organic solvents and identity of relevant degradation products	the stability of 3-methylpyrazole is stated to be uncritical		
Dissociation constant	pKa of 3.450 ± 0.012 at 20.0 ± 0.1°C pKb of 10.550 ± 0.012 at 20.0 ± 0.1°C	Anonymous 9 (2013)	OECD TG 112 GLP Rel.1
Viscosity	15.352 ± 0.001 mPa * s at 20.00 ± 0.02 °C and 5.968 ± 0.019 mPa * s at 40.00 ± 0.00 °C	Anonymous 10 (2013)	OECD TG 114 (Rolling Ball Viscosimeter) Rel.1

8 EVALUATION OF PHYSICAL HAZARDS

Not evaluated in this CLH dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Table 8: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
Toxicokinetics *in vivo* study (ADME) Gavage In rats (Wistar) : 5/sex for ADE examination, 3/sex for M analysis and 3 animals for examination of passage of placental barrier Number of exposure : single, 5 or 7 times Doses : 5 mg/kg bw (for single and 5 times) and 50 mg/kg bw (for 7 times) 3-methylpyrazole Vehicle : water Non-guideline Non-GLP	Maximal organ burden : after 30-60min Excretion : quickly (93-96% after 24h) via urine Crosses the placental barrier No bioaccumulation	No analysis of possible metabolites was performed	Anonymous 11 (1982)

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

In a toxicokinetic study (anonymous 11 (1982)), female and male rats were given by gavage 3-methylpyrazole. 5 males and 5 females received test item to examine ADE, 3 males and 3 females were

exposed to examine M and 3 animals were gavaged to analyse the passage of the placental barrier. Animals were given 5 mg/kg bw (single exposure or 5 times) or 50 mg/kg bw (7 times).

After administration, the maximal organ burden was determined after 30-60min. Thereafter, the substance is excreted via urine (93-96% within 24h). Moreover, 3-methylpyrazole crosses the placental barrier.

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity - oral route

Table 9: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels, duration of exposure	Value LD_{50}	Reference
Acute oral toxicity study Gavage OECD TG 423 GLP	Rat (CD/Crl:CD(SD)) 3 females/group	3-methylpyrazole Purity 97.9% Vehicle : 0.8% aqueous hydroxyl-methylcellulose	Conc. : 300 and 2000 mg/kg bw Observation period : 14D	LD50 : > 300 and < 2000 mg/kg bw 2000 mg/kg bw : reduced motility and muscle tone, ataxia, dyspnoea + dorsal position in all animals (+ lateral position in 2 animals) All animals died (2 within 24h and all after 7D) 300 mg/kg bw : no effects and no premature death Necropsy : no effects	Anonymous 12 (2012)

No human data or other information available

10.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

In an acute oral toxicity study (anonymous 12 (2012)), performed following OECD TG 423, groups of 3 females rats were exposed by gavage to 3-methylpyrazole. At the first step, 3 females received 2000 mg/bw. If no mortality was observed, no further testing was performed. However, if 2 out of 3 animals died, a second step was performed and 3 females were treated with 300 mg/kg bw. After this second step, if less than 2 animals died, the dose level was retested. However, if 2 out of 3 animals died, a third dose level was performed (50 mg/kg bw).

During the first step of the study, all females exhibited ataxia, dyspnoea and dorsal position, moreover, lower motility and muscle tone were observed. 2 animals died within 24h and all were dead after 7d. At necropsy, no findings were noted.

Due to the results of the first step, 3 females were exposed to 300 mg/kg bw. No mortality or clinical signs were noted. The dose level has been retested and confirmed the results.

Based on the results, the LD50 was beetwen 300 and 2000 mg/kg bw.

10.1.2 Comparison with the CLP criteria

Oral acute toxicity criteria	Results of the available study
Category 4 : LD50 between 300 and 2000 mg/kg bw	LD50 between 300 and 2000 mg/kg bw (300 mg/kg bw : no mortality ; 2000 mg/kg bw : all animals die)

10.1.3 Conclusion on classification and labelling for acute oral toxicity

Based on the available results (LD50 between 300 and 2000 mg/kg bw), a classification as **Acute Tox. Cat. 4 H302 (Harmful if swallowed)** is warranted. Furthermore, based on Table 3.1.2 of the CLP Regulation ((EC) No 1907/2006), an ATE of 500 mg/kg bw is warranted.

10.2 Acute toxicity - dermal route

No information available

10.3 Acute toxicity - inhalation route

Table 10: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, , form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
Acute inhalation toxicity study Gas Similar to OECD TG 403 Reliability 2 (study parameters not described in detail : size of test chamber, conc. Of test substance in the test chamber) however this study was considered valide No-GLP	Rat (Wistar) 5/sex/dose	3-methylpyrazole Vehicle : air	Dose levels : 2065, 3380, 4180, 7930, 18750 and 28110 mg/m³ Duration of exposure : 4h	> 28110 mg/m³ Mortality, clinical signs and necropsy examination : no effects observed	Anonymous 13 (1988)

No human data or other information available

10.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

In an acute inhalation toxicity study (anonymous 13 (1988)), similar to OECD TG 403, groups of 5 male and 5 female rats were exposed to 3-methylpyrazole at a concentration of either 2065, 3380, 4180, 7930, 18750 or 28110 mg/m³. No mortality, clinical signs or necropsy findings were observed. The LC50 was higher than 28110 mg/m³.

10.3.2 Comparison with the CLP criteria

Inhalation acute toxicity criteria	Results of the available study
Category 4 (gas) : LC50 between 2500 and 20000 ppm	One available study during which no mortality was observed (LC50 higher than 28110 mg/m³)

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Based on the results of the acute inhalation toxicity study (no mortality observed, LC50 > 28110 mg/m³), no classification is warranted.

10.4 Skin corrosion/irritation

Table 11: Summary table of other studies relevant for skin corrosion/irritation

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
In vitro/ ex vivo skin irritation study (EpiDerm) Human skin model test OECD TG 431 (no deviations)	3-methylpyrazole Purity : 98.10% Vehicle : none	Conc. : 50 µl Duration of exposure : 3 min or 1h Nb. of tissues : 2	After 3 min of exposure : Relative absorbance value : 73.8 % (threshold for corrosivity : 50 %) After 1 h of exposure : Relative absorbance value : 14.9 % (threshold for corrosivity : 15 %) Absorption value after 3min : 1.482 (negative control : 2.009; positive control : 0.586) Absorption value after 1h : 0.281 (negative control : 1.883; positive control : 0.456)	Anonymous 14 (2011)

No animal or human data available

10.4.1 Short summary and overall relevance of the provided information on skin corrosion/irritation

An *in vitro* human skin model test (anonymous 14 (2011)) was performed following OECD TG 431 (no deviations). 2 tissues were treated with 50 µl of 3-methylpyrazole during 3 min or 1 hour.

After 3 minutes of treatment, the relative absorbance value was reduced to 73.8% (above the threshold value for corrosion potential (50%)). After 1 hour of treatment, the relative absorbance value was reduced to 14.9% (below the threshold value for corrosion potential (15%)).

10.4.2 Comparison with the CLP criteria

EpiDerm criteria for classification	Results of the available study
Viability measured after exposure time points (3min and 1h) : ▪ < 50% after 3min ➔ Corrosive (optional Sub-category 1A)	In the avalaible appropriate validated *in vitro/ex vivo* human skin model test (anonymous 14 (2011)) After 3min : 73.8% After 1h : 14.9%

▪ ≥ 50% after 3min AND < 15% after 60min ➔ Corrosive (a combination of optional sub-categories 1B and 1C) ▪ ≥ 50% after 30 min AND ≥ 15% after 60min ➔ non-corrosive	➔ Corrosive substance

10.4.3 Conclusion on classification and labelling for skin corrosion/irritation

Based on the available information, a classification as **Skin corrosion Cat. 1 H314 (Causes severe skin burns and eye damage)** is warranted.

10.5 Serious eye damage/eye irritation

Table 12: Summary table of other studies relevant for serious eye damage/eye irritation

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
In vitro/ex vivo eye irritation study BCOP test Bovine eye OECD TG 437	3-methylpyrazole Purity : 98.10% Vehicle : /	Conc. : 750 µl Duration of exposure : 10min Nb. of tissues : 3	IVIS : Test item : 85.73 Positive control : 215.79 Negative control : - 0.216	Anonymous 15 (2011)

No animal or human data available

10.5.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

An *in vitro* eye irritation study, BCOP test (anonymous 15 (2011)), was performed following OECD TG 437. 3 tissues were treated with 750 µl of 3-methylpyrazole during 10 min.

The *in vitro* irritancy score was 85.73 for the test substance (215.79 for the positive control and -0.216 for the negative control).

10.5.2 Comparison with the CLP criteria

OECD TG 437 criteria	Results of the available study
IVIS : ▪ ≤ 3 : no category ▪ > 3 and ≤ 55 : no prediction can be made ▪ > 55 : Category 1	The appropriate validated *in vitro* eye irritation study (anonymous 15 (2011)) revealed an IVIS of 85.73

10.5.3 Conclusion on classification and labelling for serious eye damage/eye irritation

Based on the available results, a classification as **Eye damage Cat. 1 H318 (Causes serious eye damage)** is warranted.

10.6 Respiratory sensitisation

No information available

10.7 Skin sensitisation

Not evaluated in this CLH report.

10.8 Germ cell mutagenicity

Not evaluated in this CLH report.

10.9 Carcinogenicity

Not evaluated in this CLH report.

10.10 Reproductive toxicity

10.10.1 Adverse effects on sexual function and fertility

No information available

10.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

No two-generation or extended one-generation toxicity study is available. Furthermore, the repeated dose toxicity studies (see chapter 10.12) do not indicate lesions in the reproductive organs.

10.10.3 Comparison with the CLP criteria

Criteria for Category 1	Criteria for Category 2	Results of the available studies
"known or presumed human reproductive toxicant. Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. Category 1A : the classification is largely based on evidence from humans Category 1B : the classification is largely	"Suspected human reproductive toxicant. Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, category 2 could be more appropriate classification. Such effects shall have been observed in the	No two-generation or extended one-generation toxicity study is available. However, the repeated dose toxicity studies do not indicate lesions in the reproductive organs. No classification warranted due to lack of data

based on data from animals studies. Such data shall provide clear evidence of an adverse effect on sexuakl function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered no to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in category 2 may be more appropriate."	absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects."	

10.10.4 Adverse effects on development

Table 13: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Developmental toxicity study Rat (Wistar) 25 pregnant females/group OECD TG 414 GLP	3-methylpyrazole Purity : 99.9% Vehicle : water Gavage Conc. : 0, 15, 45 and 90 mg/kg bw/d Duration of exposure : GD 6-15	Dams : 90 mg/kg bw/d : decrease food consumption + significant lower bw and uterus weight 45 mg/kg bw/d : decrease food consumption + ↓ bw Foetuses : 90 mg/kg bw/d : lower foetal bw Delayed ossification + malformation of the urogenital tract, cardio-vascular system and thoracic vertebral bodies 45 mg/kg bw/d : significant decrease foetal bw No teratogenic effects	Anonymous 16 (1992)
Developmental toxicity study Rat (Wistar) Nb. of animals : not specified No guideline followed No info on the GLP status	3-methylpyrazole Purity : unknown Vehicle : water Oral (no more information) Conc. : 0, 20, 40, 80 and 160 mg/kg bw/d Duration of exposure : 10 and 11 dpc	Dams : No effects observed Fetuses : 160 mg/kg bw/d : significant lower viability and live birth indices. Necropsy revealed urogenital syndrome 80 mg/kg bw/d : urogenital malformation (uni and bi-lateral kidney agenesis, hydronephrosis)	Bleyl D.W.R (1990)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Prenatal toxicity study Rat (Wistar) Nb of animals : 13, 13, 12, 14 and 6 rats (respectively at 0, 50, 10, 200 and 400 mg/kg bw/d) No guideline followed No GLP information	3-methylpyrazole Purity : unknown Vehicle : water Oral (by stomach tube) Conc. : 0, 50, 100, 200 and 400 mg/kg bw/exposure Day of exposure : GD 1, 4, 10, 13, 18 and 20	Dams : 400 mg/kg bw/exposure : 4 rats died prematurely Significantly bw changes Significant increase of the post implantation loss (higher resorption rate 75% vs 12-15% in the other groups) 200 mg/kg bw/exposure : significantly bw changes NOAEL : 100 mg/kg bw/exposure Fetuses : 400 mg/kg bw/exposure : significantly lower fetal weight + placental weight modified 200 mg/kg bw/exposure : significantly lower fetal weight Dose dependent increased malformation rate : 11%, 46% and 100% respectively at 100, 200 and 400 mg/kg bw/exposure (severe alteration of the urogenital tract) NOAEL : 50 mg/kg bw/exposure	Anonymous 17 (1984)
Prenatal toxicity study Rat (strain unknown) 8 pregnant females/group No guideline followed No GLP information	3-methylpyrazole Oral (stomach tube) Conc. : 0, 25, 100, 175 and 225 mg/kg bw/d Duration of exposure : GD 6-18	Dams : 225 mg/kg bw/d : all animals died or had to be killed prematurely 175 mg/kg bw/d : 6 out of 8 animals died or had to be killed prematurely. The 2 surviving animals had no live fetuses 100 mg/kg bw/d : bw changes Higher resorption rate Fetuses : 100 mg/kg bw/d : severe decrease of the fetal bw 1 fetus exhibited a cleft palate	Anonymous 18 (1989)

No human data or other information available

10.10.5 Short summary and overall relevance of the provided information on adverse effects on development

In a developmental prenatal toxicity study (anonymous 16 (1992)), performed following OECD TG 414, groups of 25 pregnant rats were given 3-methylpyrazole at a concentration of 0, 15, 45 or 90 mg/kg bw/d through gestation day 6 to 15. On day 20 post-coitum, all females were sacrified and necropsied.

No mortality or clinical signs were observed. Mean body weight was significantly lower at the highest doses. Furthermore, the corrected body weight (bw at GD20 minus uterus weight minus bw at GD6) was significantly reduced in the animals exposed to 90 mg/kg bw/d. At necropsy, the uterus weight was significantly decreased at the highest dose and only one dam of the lowest dose exhibited a hydrometra.

Table 14 : Body weight data in g (in g)(extent of the changes in % with respect to the controls)

Dose level (in mg/kg	0	15	45	90

bw/d)				
GD 0	225.0	222.4 (-1.16)	223.7 (-0.58)	224.9 (-0.04)
GD 6	254.5	250.8 (-1.45)	253.1 (-0.55)	252.3 (-0.86)
GD15	300.0	295.0 (-1.67)	292.2 (-2.6)	276.4** (-7.87)
GD20	373.3	368.4 (-1.31)	364.2 (-2.44)	352.6** (-5.55)
BWG GD 6-15	45.6	44.1 (-3.29)	39.1 (-14.25)	24.1** (-47.15)
BWG GD 0-20	148.3	146.0 (-1.55)	140.4 (-5.33)	127.7** (-13.89)
Gravid uterus weight	81.0	79.7 (-1.60)	75.2 (-7.16)	69.1** (-14.69)
Net weight change from D6	37.8	37.8	35.8 (-5.29)	31.2* (-17.46)

* $p < 0.05$; ** : $p < 0.01$

The reproductive data were unaffected (such as conception rate, mean number of corpora lutea, implantation sites, pre- and post-implantation loss, number of resorption and viable foetuses).

Table 15 : reproduction data

Dose level (in mg/kg bw/d)		0	15	45	90
Nb of females mated		25	25	25	25
Nb of females pregnant		24	22	25	25
Dams with viable fetuses		24	22	25	25
Mean nb of corpora lutea		15.7	15.5	15.5	15.8
Mean nb of implantation sites		15.3	14.9	14.5	14.7
Mean % of preimplantation loss		2.3	3.8	6.2	6.5
Mean % of postimplantation loss		8.1	5.8	5.6	7.8
Mean resorptions	Tot.	1.3	0.9	0.8	1.2
	Early	1.2	0.7	0.8	1.0
	Late	0.0	0.2	0.0	0.1
Nb of dead fetuses		0	0	0	0
Mean nb of live fetuses		14.1	14.0	13.7	13.6

Examination of the foetuses did not reveal a difference in the sex distribution (51.5/48.5, 48.7/51.3, 50.1/49.9 and 47.2/52.8% of females/males respectively at 0, 15, 45 and 90 mg/kg bw/d) or in the placental weight (0.45, 0.46, 0.46 and 0.43g respectively at 0, 15, 45 and 90 mg/kg bw/d). However, the mean fetal weight was significantly lower at the 2 highest dose levels (3.9, 3.8, 3.6** and 3.3**g respectively at 0, 15, 45 and 90 mg/kg bw/d). One foetus of one dam which was exposed to 45 mg/kg bw/d exhibited a cleft palate. Soft tissue examination revealed severe malformations in the urogenital tract and/or in the cardiovascular system in the foetuses of the highest dose. Various malformations of the sternum and/or the vertebral column were also observed in all groups.

Table 16 : Incidence of fetal soft tissue malformations

Dose level (in mg/kg bw/d)	0	15	45	90
Nb. of foetuses evaluated (Nb. of litters evaluated)	164 (24)	149 (22)	166 (25)	163 (25)
Fetal incidence (tot nb)	0	0	0	14**

Litter incidence (tot nb)		0	0	0	8**
Efferent urinary tract severely dilated (litter incidence)	Fetal incidence (%)	0	0	0	5* (3.1)
	Litter incidence (%)	0	0	0	5 (20)
Malformation of great vessels (displaced aortic arch) (litter incidence)	Fetal incidence (%)	0	0	0	6* (3.7)
	Litter incidence (%)	0	0	0	2 (8.0)
Agenesie of kidney(s) (litter incidence)	Fetal incidence (%)	0	0	0	2 (1.2)
	Litter incidence (%)	0	0	0	2 (8.0)
Agenesie of ureter(s) (litter incidence)	Fetal incidence (%)	0	0	0	2 1.2)
	Litter incidence (%)	0	0	0	2 (8.0)
Dilatation of both ventricles (globular shaped heart) (litter incidence)	Fetal incidence (%)	0	0	0	2 (1.2)
	Litter incidence (%)	0	0	0	2 (8.0)

* $p < 0.05$; ** : $p < 0.01$

Table 17 : Incidence of skeletal malformations

Dose level (in mg/kg bw/d)		0	15	45	90	Historical data in %
Nb. of foetuses evaluated (Nb. of litters evaluated)		174 (24)	159 (22)	177 (25)	176 (25)	
Fetal incidence		8	8	8	49**	
Litter incidence		6	6	5	20**	
Thoracic vertebral body/bodies dumbbell-shaped (%)	Fetal incidence (%)	6 (3.4)	5 (3.1)	3 (1.7)	39** (22)	0 – 8.8
	Litter incidence (%)	4 (17)	5 (23)	2 (8)	17** (68)	0 – 39.1
Thoracic vertebral body/bodies bipartite (%)	Fetal incidence (%)	0	1 (0.6)	4 (2.3)	16** (9.1)	0 - 1.6
	Litter incidence (%)	0	1 (4.5)	2 (8.0)	10** (40)	0 – 9.5

** : $p < 0.01$; no more information on the historical control data

In another developmental toxicity study (article : Bleyl DWR, 1990), groups of pregant Wistar rats (number of animals not mentioned) were exposed on GD 10 and 11 only to 3-methylpyrazole at a concentration of 0, 20, 40, 80 or 160 mg/kg bw/d.

Regarding dams, no effects was observed on the body weight or the liver weight after 20 days (no more information available).

At the highest dose level, the rate of living pups at birth was significantly reduced (77%* compared to the control group). Moreover, most of these living pups died in the first day of live. The survival index (at PND4) was 26%**. 15.6% of the living fetuses in the 80 mg/kg bw/d dose level group exhibited urogenital syndrome. In most cases, an unilateral kidney agenesis was noted (no left kidney) coupled with a hydronephrosis in the remaining kidney. The other pups exhibited a bilateral kidney agenesis. In males, the genital tract was complete, however some cases of undescended testis were recorded. Whereas in females, the kidney agenesis was always coupled with an incomplete differentiation of the uterus. The necropsy of the

fetuses of the highest dose level, which died in the first day of live, revealed also the urogenital syndrome. (no more information available)

On PND 43 for males and PND 44 for females, the renal function of the surviving pups has been investigated and revealed disturbances in females at the 2 highest dose levels only.

In another prenatal developmental toxicity study (anonymous 17, 1984), groups of pregnant Wistar rats were given by gavage 3-methylpyrazole at a concentration of 0, 50, 100, 200 and 400 mg/kg bw/exposure. Groups were composed of 13, 13, 12, 14 and 6 females rats respectively at 0, 50, 100, 200 and 400 mg/kg bw/exposure.

4 dams exposed to the highest dose level died during the exposure period. The necropsy of these animals revealed a catarrhal enteritis and/or nephrosis syndrome. Moreover, a significant decrease of the body weight was observed at this dose level. A trend to decrease was also observed at the 200 mg/kg bw/exposure level.

Table 18 : Body weight (in g)

Dose (mg/kg bw/d)	Body weight (g)					
	GD1	GD4	GD10	GD13	GD18	GD20
0	268 ± 8	276 ± 7	288 ± 8	298 ± 9	387 ± 9	334 ± 9
50	245 ± 7	257 ± 8	273 ± 9	279 ± 10	309 ± 18	328 ± 11
100	255 ± 7	262 ± 7	280 ± 8	283 ± 10	315 ± 7	292 ± 33
200	251 ± 5	260 ± 6	270 ± 6	275 ± 7	298 ± 7	306 ± 8*
400	253 ± 15	264 ± 15	263 ± 15	256 ± 16**	246 ± 15**	258 ± 15**

* = p<0.05, ** = p<0.01

The necropsy of dams did not reveal absolute liver weight modifications, only a slight dose related increase relative liver weight (absolute liver weight : 12.2, 12.5, 13.1, 12.1 and 11.3 g respectively at 0, 50, 100, 200 and 400 mg/kg bw/exposure; relative liver weight : 2.6, 3.8, 3.9, 4.0 and 4.2 g/100g bw respectively at 0, 50, 100, 200 and 400 mg/kg bw/exposure).

No effects on the pre-implantation loss was recorded. Nevertheless, percentage of post-implantation loss was significantly increased at the highest dose level (11.5, 13.8, 11.8, 14.9 and 74.9**%** respectively at 0, 50, 100, 200 and 400 mg/kg bw/exposure). Furthermore, in 4 out of 6 dams of the highest dose level, all progeny died by resorptions.

Table 19 : Resorptions and dead foetus (in %)

Dose level (in mg/kg bw/d)	0	50	100	200	400
Early	9.6	6.7	10.1	10.5	2.5
Middle	1.9	7.1	0	3.0	69.8**
Late	0	0	0	0.5	0
Dead foetus	0	0	0	0.5	2.6*
MS calculated summation	11.5	13.8	10.1	14.5	74.9

** : p < 0.01

The apparent discrepancies between the reported % of post-implantation loss and the MS calculated summation (resopriotns and dead foetus) come directly from the data specified in the full study report (anonymous 17, 1984, page 19), BE CA transcribes the same data in the current document.

Regarding the foetal examination, the body weight was significantly reduced at the 2 highest dose levels (1.80, 1.80, 1.70, 1.40** and 1.05**g respectively at 0, 50, 100, 200 and 400 mg/kg bw/d). The placental weight was also modified (0.43, 0.46, 0.46, 0.41 and 0.28g** respectively at 0, 50, 100, 200 and 400 mg/kg bw/exposure). All fetuses of the highest dose presented at least one malformation (46.8% at 200 mg/kg bw/exposure and 11.1% at 100 mg/kg bw/exposure).

Table 20 : Malformation data (in %)

Dose (mg/kg)	0	50	100	200	400
Syndactilie/Retrodactilie					
Total	0	0	1.2 ± 0.8	15.3 ± 6.3§	81.3 ± 18.8§
Forelimb	0	0	1.2 ± 0.8	14.0 ± 6.5§	81.3 ± 18.8§
Hind limb	0	0	0	4.6 ± 3.4	50.0 ± 37.5§
Amelia	0	0	0	1.2 ± 0.8	6.3 ± 6.3
Anemia	0	0	0	2.6 ± 1.5+	0
Cleft palate	0	0	0	0.5 ± 0.5	12.5 ± 12.5
Urogenital syndrome					
Total	0	0	4.4 ± 4.4	40.8 ± 8.0§	58.8 ± 31.3§
Symmetric	0	0	3.3 ± 3.3	27.6 ± 8.5§	50.4 ± 25.0§
Asymmetric	0	0	1.1 ± 1.1	13.2 ± 3.0	31.3 ± 6.3§
Hydronephrose	0.5 ± 0.5	2.0 ± 1.0	5.1 ± 2.4+	1.9 ± 1.0	0
Ecchymosis	0.5 ± 0.5	0	3.8 ± 2.6	1.2 ± 0.8	0
Horizonal cardiac apex	0	0	2.8 ± 1.5	4.2 ± 1.9	6.3 ± 6.3
Total (%)	0.5 ± 0.5	2.0 ± 1.0	11.1 ± 4.5	46.8 ± 6.8§	100 ± 0.1§

+ = $p<0.05$, § = $p<0.01$

In another developmental toxicity study (anonymous 18, 1989), groups of 8 pregnant rats were received by gavage 3-methylpyrazole at a concentration of 0, 25, 100, 175 and 225 mg/kg bw/d. Animals were exposed from GD 6 to 18 and were sacrified at GD20.

6 out of 8 dams exposed to 175 mg/kg bw/d and all dams exposed to 225 mg/kg bw/d died or were sacrificed in extremis respectively. Regarding the animals receiving 100 mg/kg bw/d of 3-methylpyrazole, moderate to severe decrease body weight was noted during GD 6-12. Furthermore, an increase in resorptions was noted at this dose level and no fetus was produced by the 2 females of the 175 mg/kg bw/d group which survived.

Regarding the fetuses examination, the fetal weight was reduced in the 100 mg/kg bw/d group. Moreover, one fetus of this group exhibited external malformations such as cleft palate. However, this fetus weighted only 1.2 g.

10.10.6 Comparison with the CLP criteria

Criteria for Category 1	Criteria for Category 2	Results of the available studies
"known or presumed human reproductive toxicant. Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on	"Suspected human reproductive toxicant. Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly	See above

development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. Category 1A : the classification is largely based on evidence from humans Category 1B : the classification is largely based on data from animals studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered no to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in category 2 may be more appropriate."	supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, category 2 could be more appropriate classification. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects."	

In the developmental prenatal toxicity study (anonymous 16 (1992)), dams exhibited a significant decrease of body weight only at the highest dose level (90 mg/kg bw/d). At this dose level, severe fetal malformations in the urogenital tract and/or in cardiovascular system were observed. The incidence of these malformations was significantly higher at the highest dose (14 foetus exhibited malformations vs 0 in the other groups). In 2 out of these animals, an agenesis of kidney was noted. Furthermore, skeletal malformations were also observed and were outside the range of the historical control data. In addition to that a significant decrease of the fetal body weight was already observed at the mid dose level (45 mg/kg bw) which cannot be explained by any parental toxicity.

Moreover, in another developmental toxicity study (Bleyl DWR, 1990), dams did not show any maternal toxicity. Nevertheless, the rate of living pups at birth was significantly reduced and most of the living pups died during the first day of life. Pups exhibited severe urogenital malformations (kidney(s) agenesis and/or hydronephrosis).

In another developmental toxicity study (anonymous 17 (1984)), maternal toxicity was observed at the highest dose level (400 mg/kg bw/d). However, a significant increase incidence of fetal malformation (urogenital syndrome) was already observed at 200 mg/kg bw/d. Moreover, an increase incidence of cleft palate and a significant increase incidence of post-implantation loss were observed at 400 mg/kg bw/d.

3 different studies revealed severe malformations of the urogenital tract already at dose levels where no maternal toxicity was observed. Those malformations vary from severe dilatation of the efferent urinay tract and malformations of great vessels to the complete absence of kidney. Therefore, the criteria for the category 1B is fulfilled.

10.10.7 Adverse effects on or via lactation

No information available

10.10.8 Conclusion on classification and labelling for reproductive toxicity

Based on the available information, a classification as **Repr. 1B H360D (May cause damage on unborn child)** is warranted.

10.11 Specific target organ toxicity-single exposure

Not evaluated in this CLH dossier

10.12 Specific target organ toxicity-repeated exposure

Table 21: Summary table of animal studies on STOT RE

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
Short-term oral toxicity study Mouse (B6C3F1) 5/sex/dose OECD TG 407 GLP	3-methylpyrazole (purity : 99.7%) Via drinking water Conc. : 0, 900, 1125 and 1575 ppm (corresponding to 0/0, 135/173, 153/198 and 167/245 mg/kg bw/d respectively in males/females) Duration of exposure : 28d	Mortality and clinical signs : no effects Bwg : change in ♀ (bw : unaffected) ↑ lung weight (abs. and rela.) Histopathology : change in lungs in all animals (karyomegaly in the epithelium of the air ducts, loss of domes in the Clara cells, hypotrophy of the air duct epithelia) No NOAEL identified	Anonymous 19 (1996)

Short-term oral toxicity study Mouse (B6C3F1) 5/sex/dose for main groups + 5/sex/dose for recovery groups (14D of recovery) EU Method B.7 GLP	3-methylpyrazole (purity : 99.4%) Via drinking water Conc. : 300, 900 and 1575 ppm (± 0/0, 70/82, 151/193 and 223/252 mg/kg bw/d in males/females at 0, 300, 900 and 1575ppm) Duration of exposure : 28d Recovery period : 14d	300 ppm : slight ↓ food and water consumption in ♀ ↑ lung weight in ♀ Moderate Clara cell alteration in ♂/♀ 900 ppm : tremor and hunched posture in ♀ ↓ bwg in ♀ and ↓ food and water consumption in ♂/♀ ↑ lung weight in ♂/♀ Moderate Clara cell alteration in ♂/♀ Parenchymal lung changes in a few mice 1575 ppm : tremor and hunched posture in ♀ ↓ bw, food and water consumption in ♂/♀ ↑ lung weight in ♂/♀ Moderate to marked Clara cell alteration in ♂/♀ Parenchymal lung changes in a few mice Complete recovery not accomplished in a 14 D follow up period No NOAEL identified	Anonymous 20 (1997)
Short-term oral toxicity study Mouse (B6C3F1) 3/sex/dose Non-guideline Non-GLP	3-methylpyrazole (purity : 99.77%) Via drinking water Conc. : 0, 225 and 675 ppm (corresponding to 0/0, 47/61 and 140/173 mg/kg bw/d in males/females) Duration of exposure : 2w	Mortality, clinical signs, bw, organ weight, gross pathology, histopathology : no treatment-related effects NOAEL : > 675 ppm	Anonymous 21 (1996)
Subchronic oral toxicity study Rat (Wistar) 10/sex/dose for main groups (+ 10/sex/dose for recovery groups (28D of recovery) OECD TG 407 and 408 GLP	3-methylpyrazole (99.34%) Via drinking water Conc. : 0 and 40 mg/kg bw/d Duration of exposure : 90d Recovery period : 28d	Mortality, clinical signs and bw : no effects Organ weight examination (kidneys, liver and lungs) : ↑ kidney and liver weights (abs. + rela.) in ♀ but fully reversible at the end of the recovery period Histopathology examination (kidneys, liver and lungs) : no treatment-related effects NOAEL : 40 mg/kg bw/d	Anonymous 22 (1999)

Subchronic oral toxicity study Rat (Wistar) 24/sex/dose (exception : 36/sex for control group) Non-guideline Non-GLP	3-methylpyrazole Via gavage Conc. : 0, 0.2, 2, 20 and 200 mg/kg bw/d Duration of exposure : 90d	200 mg/kg bw/d : ↓ bw and food consumption in ♂/♀ Hematology and clinical biochemistry : ↑ nb. of neutrophilic lymphocytes, ASAT, ALP activity, ↓ tot. prot., albumin, glucose in both sexe and ↓ ChE activity in ♀ Organ weight : lower brain, spleen, thymus and testes weight and higher liver weight at the highest dose level Alteration thyroid glands Liver : nucleus anisomorphism, fatty degeneration and cell death NOAEL : 20 mg/kg bw/d	Anonymous 23 (1980)
Subchronic oral toxicity study Mouse (B6C3F1) 10/sexe/dose + 10/sex/groups for recovery groups OECD TG 408 GLP	3-methylpyrazole (purity : 98.38%) Via drinking water Conc. : 0, 5, 10, 20 and 40 mg/kg bw/d Duration of exposure : 13w Recovery period 4w	Mortality, clinical signs, hematology, clinical biochemistry, organ weight : no effects Sign. lower bw in males in all dose levels Histopathology : ≥ 10 mg/kg bw/d : Clara cell alteration (mix degenerative and regenerative process)	Anonymous 24 (2000)
Chronic oral toxicity study Rat (Wistar) 32/sex/group Non-guideline Non-GLP	3-methylpyrazole Via drinking water Conc. : 0, 10, 40 and 2000/1000 ppm (2000ppm during w1-4 thereafter 1000ppm w5-80) Duration of exposure : 18m	High mortality rate in all groups ≥ 10 ppm : dyspnea, cachexia, pneumonia 2000/1000 ppm : ↓ bw (♂ 82.3 % and ♀ 70.6 % of control group), food and water consumption, erythrocyte, Hb and Ht ↑ aminotransferase, lucine aminopeptidase, alkaline phosphatase, inhibition activity of cholinesterase (♀), cholesterol ↑ heart, liver, kidneys, brain and thyroid weight Histopathology : focal alteration in liver Ovaries : no effects on follicular maturation and evolution of Corpus luteum Testis : no effects on spermiogenesis	Anonymous 25 (1985)

No human data or other information available

10.12.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure

In a short term toxicity study (anonymous 19 (1996)), performed following OECD TG 407, 3-methylpyrazole was given via drinking water to groups of 5 male and 5 female mice at a concentrations of 0, 900, 1125 or 1575 ppm during 4 weeks. The concentration in the drinking water correspond to a mean daily test substance intake of 0, 154, 176 and 206 mg/kg bw/d respectively at 0, 900, 1125 and 1575 ppm.

No mortality and no clinical signs were noted during the study. Body weight was unaffected in all dose levels (29.3/23.7, 28.6/23.7, 28.0/23.7 and 28.7/22.9g in males/females respectively at 0, 900, 1125 and 1575 ppm), however body weight gain was significantly lower in females of the highest dose level (BWG 0-28D : 4.3/4.6, 3.5/4.1, 3.0/4.2 and 3.8/3.4** g in males/females respectively at 0, 900, 1125 and 1575 ppm).

Necropsy revealed a significant higher lung weight in both sexes at the highest dose level and in males at the lowest dose level. Liver weight was significantly reduced at 1125 ppm in male. The relative organ weight observation showed only changes in lung. Histopathology examination was only performed on the lungs. Lesions of the mucus cells of the air ducts and of the Clara cells in the bronchi and bronchioles were recorded. Clara cells alteration consisted of moderate to severe disorganization of the luminal lining cell layer due to flattening of the cells and loss of the apical parts of the Clara cells and due to development of irregular shaped clara cell nuclei. Moreover, hypotrophy of the air duct epithelia (focal or diffuse) was recorded (see table 22).

Table 22 : Organ weight data

		Males				Females			
Dose level (in ppm)		0	900	1125	1575	0	900	1125	1575
Number of animals examined		5	5	5	5	5	5	5	5
Organ weights									
FBW (in g)		24.86	23.78	22.84	23.4	18.82	20.16	20.08	19.12
Kidneys weight (in mg and %)	abs	486.6	471	457.8	462.6	360.2	358.6	366.8	357.2
	Rela	1.958	1.978	2.004	1.975	1.915	1.779	1.825	1.869
Liver weight (in mg and %)	abs	1081	1012.8	958**	1043.4	894.8	975.4	989	989.6
	Rela	4.354	4.257	4.194	4.449	4.741	4.838	4.923	5.175
Lungs weight (in mg and %)	Abs	224	330*	418.6	353.6*	215	287.4	312.4	334.8**
	rela	0.898	1.392*	1.833*	1.53*	1.142	1.422	1.554	1.755
Gross lesions									
Erosion/ulcer in glandular stomach : incidence		0	3	4	4	3	4	4	5
Histopathology : changes in lungs									
Clara cell lesion	incidence	0	5	5	5	0	5	5	5
	Karyomegaly : incidence by grade 3/4	0/0	1/4	0/5	1/4	0/0	0/5	2/3	1/4
	Loss of domes : incidence	0	5	5	5	0	5	5	5
Hypotrophy focal		0	4	2	2	0	0	0	1
Hypotrophy diffuse		0	1	3	3	0	5	5	4

* : $p < 0.05$; ** : $p < 0.01$

In a short-term oral toxicity study (anonymous 20 (1997)), performed following EU method B.7, groups of 5 male and 5 female mice (B6C3F1) (main groups) were exposed via drinking water to 3-methylpyrazole at a concentration of 0, 300, 900 or 1575 ppm during 28 days, corresponding to 0/0, 70/82, 151/193 or 223/252 mg/kg bw/d respectively in males/females. Additionally, 5 males and 5 females (recovery groups) were exposed to the same dose levels during 28 days and were examined during a recovery period of 14 days.

No mortality occurred during the study period. Females of the mid and high dose level exhibited tremors and/or hunched posture. The body weight examination revealed a statistically significant lower value in females at the highest dose. The body weight gain was already decreased in females at 900 ppm and in males at 1575 ppm. However, during the recovery period, no differences in body weight were observed.

Table 23 : Body weight (in g)

	Males				Females			
Dose level (in ppm)	0	300	900	1575	0	300	900	1575
Exposure period								
Number of animals examined	10	10	10	10	10	10	10	10
D1	23.7	23.7	24.2	24.0	19.1	19.5	19.4	19.6
D15	25.7	26.2	25.7	25.7	21.4	21.9	20.8	20.4
D29	26.8	27.6	26.5	25.5	23.4	23.8	22.3	21.7**
BWG D0 – D29	13	16	10	6*	23	22	15**	11**
Recovery period								
Number of animals examined	5	5	5	5	5	5	5	5
D8	27.8	26.8	27.2	27.0	23.0	24.4*	23.4	22.4
D16	29.0	27.8	28.6	28.0	24.0	25.2	24.0	24.2

* : $p < 0.05$; ** : $p < 0.01$

Animals of the main groups were killed after 28 days of exposure. Macroscopic observations did not reveal any treatment-related changes. However, the absolute lung weight was increased in females at the mid and high dose level, whereas the relative lung weight was already increased in females at the low dose level and was also increased in males at the mid and high dose level. Whereas, the necropsy of animals of the recovery groups revealed that the absolute lung weight was increased in females at the mid dose level while the relative lung weight was increased in females at 900 and 1575 ppm.

The microscopic examination of the main groups revealed a Clara cell alteration (moderate at 300 and 900 ppm, and moderate to marked at 1575 ppm). This modification was characterized by a loss of the characteristic dome-shaped appearance and the apical “bled”, by cytokaryomegaly, and basophilia. Furthermore, at 1575 ppm, mitotic figures and/or macrophages were noted in the altered epithelium of the bronchi and bronchioli. In a few mice of the mid and high dose levels, interstitial histiocytosis, alveolar macrophages, alveolar hemorrhage, alveolar edema and/or interstitial edema/congestion were observed. The animals of all recovery groups showed also a Clara cell alteration (slight to moderate at 300 and 900 ppm and moderate to marked at 1575 ppm). In addition, slight to moderate Clara cell proliferation (characterized by increased numbers cytokaryomegalic, basophilic and sometimes multinuclear cells) was observed in all treated mice of these groups. These cells were arranged in two cell layers instead of the normal one layer. In addition, mitotic figures were occasionally observed.

Table 24 : Organ weight and histopathological modifications

		Males				Females			
Dose level (in ppm)		0	300	900	1575	0	300	900	1575
Main groups (5 mice/sex/dose)									
Absolute lungs weight (in g)		0.208	0.207	0.234	0.239	0.177	0.226	0.263**	0.249**
Relative lungs weight (in %)		0.839	0.807	0.970*	0.983*	0.794	1.006*	1.255**	1.178**
Clara cell alteration	Incidence	0/5	5/5	5/5	5/5	0/5	5/5	5/5	5/5
	Grade 2							1/5	
	Grade 3		5/5	5/5	2/5		5/5	3/5	4/5

	Grade 4				3/5			1/5	1/5
Interstitial histiocytosis incidence (grade 2)		0/5	0/5	0/5	3/5	0/5	0/5	1/5	1/5
Alveolar macrophages (grade 2)	Incidence	0/5	0/5	1/5	3/5	0/5	0/5	0/5	2/5
Alveolar hemorrhage	Incidence	0/5	0/5	2/5	4/5	0/5	0/5	2/5	2/5
	Grade 2			2/5	4/5			1/5	2/5
	Grade 3							1/5	
Alveolar edema incidence (grade 1)		0/5	0/5	0/5	0/5	0/5	0/5	0/5	1/5
Interstitial edema/congestion	Incidence	0/5	0/5	1/5	3/5	0/5	0/5	0/5	2/5
	Grade 1								1/5
	Grade 2			1/5	3/5				1/5
Recovery groups (5 mice/sex/dose)									
Absolute lungs weight (in g)		0.187	0.203	0.207	0.203	0.185	0.196	0.237**	0.221
Relative lungs weight (in %)		0.664	0.761	0.762	0.749	0.818	0.852	1.030**	0.977*
Clara cell alteration	Incidence	0/5	5/5	5/5	5/5	0/5	5/5	5/5	5/5
	Grade 2		3/5					1/5	
	Grade 3		2/5	5/5	2/5		5/5	4/5	4/5
	Grade 4				3/5				1/5
Clara cell proliferation	Incidence	0/5	5/5	5/5	5/5	0/5	5/5	5/5	5/5
	Grade 2		2/5	2/5	3/5		1/5	5/5	
	Grade 3		3/5	3/5	2/5		4/5		5/5
Alveolar macrophages incidence (grade 2)		0/5	0/5	0/5	0/5	0/5	0/5	0/5	1/5
Alveolar hemorrhage	Incidence	0/5	0/5	1/5	1/5	0/5	0/5	0/5	0/5
	Grade 2				1/5				
	Grade 3			1/5					

* : $p < 0.05$; ** : $p < 0.01$
Grade 1 : minimal/very few/very small ; Grade 2 : slight/few/small ; grade 3 : moderate/moderate number/moderate size ; Grade 4 : marked/many/large

In a short-term repeated dose toxicity study (anonymous 21 (1996)), groups of 3 male and 3 female mice were exposed via drinking water to 3-methylpyrazole at a concentration of 0, 225 or 675 ppm during 2 weeks. The concentration in the drinking water corresponded to a test substance intake of 0/0, 47/61 and 140/173 mg/kg bw/d respectively in males/females.

No mortality and no clinical signs were recorded. Body weight examination did not reveal significant changes (at D14 : 25.0/21.0, 25.2/21.2 and 25.7/21.3 g respectively at 0, 225 and 675 ppm).

Erosions/ulcers in the glandular stomach and discoloration of contents of the jejunum were observed in all groups (in 0/2 , 0/2 and 3 males/3females respectively at 0, 225 and 675 ppm).

In a subchronic toxicity study (anonymous 22 (1999)), following OECD TG 407 and 408, groups of 10 male and 10 female rats (Wistar) (main groups) were exposed via drinking water to 3-methylpyrazole at a

concentration of 0 or 40 mg/kg bw/d during 90 days. Additionally, 10 males and 10 females (recovery groups) were exposed to the same dose levels during 90 days and were examined during a recovery period of 28 days.

No mortality, no clinical signs and no body weight modification occurred during the study period.

The organ weight and histopathology examination were performed on kidneys, liver and lungs. Significant increase in absolute and relative kidneys weight was noted in females (slight trend in males). Moreover, significant increase of liver weight (abs. and rela.) was observed in females. These changes did not appear at the end of the recovery period. 2 males of the control group and 1 male exposed to 40 mg/kg bw/d showed intracellular vacuoles in hepatocytes (low grade).

Table 25 : Organ weight

		Main groups				Recovery groups			
		Males		Females		Males		Females	
Dose level (mg/kg bw/d)		0	40	0	40	0	40	0	40
Kidney (left) weight (in mg)	Abs	1572.0	1602.8	1046.9	1166.3*	1679.5	1628.1	1088.3	1025.5
	Rela	0.3174	0.3356	0.3591	0.4006*	0.3294	0.3177	0.3420	0.3445
Kidney (right) weight (in mg)	Abs	1562.8	1595.3	1046.7	1183.8*	1653.6	1622.5	1067.7	1021.7
	Rela	0.3150	0.3347	0.3588	0.4069*	0.3239	0.3154	0.3349	0.3432
Liver weight (in mg)	Abs	20229.8	19642.3	11151.3	12594.8*	20788.0	18629.9	11149.9	9715.6*
	Rela	4.080	4.107	3.799	4.293*	4.036	3.596	3.474	3.271
Lungs weight (in mg)	Abs	2369.1	2241.0	1763.6	1865.4	2294.0	2234.1	1763.8	1731.7
	rela	0.4817	0.4692	0.6011	0.6381	0.4492	0.4346	0.5556	0.5823

* $p < 0.05$

In a subchronic toxicity study (anonymous 23 (1980)), rats were exposed to 3-methylpyrazole at a concentration of 0, 0.2, 2, 20 or 200 mg/kg bw/d during 90 days. Treated groups were composed of 24 females and 24 males and control groups were composed of 36 females and 36 males.

Only 2 males died during the study (1 exposed to 20 mg and 1 exposed to 200 mg/kg bw/d). The body weight decreased at the highest dose level, the modification was more severe in males.

Table 26 : Body weight data

	Males					Females				
Dose level (in mg/kg bw/d)	0	0.2	2	20	200	0	0.2	2	20	200
W0	78	78	76	76	76	72	73	72	72	71
W6	270	283	276	274	198	201	200	202	200	168
W12	359	372	362	359	262	249	248	249	246	222

Changes were noted during enzyme activity examination. At the highest dose level, aspartate aminotransferase, leucine aminotransferase and alkaline phosphatase activity were increased. Cholinesterase activity was reduced only in females at the highest dose level. (See table 27)

Table 27 : Enzyme activity data after 12w

Dose level (mg/kg bw/d)	Males					Females				
	0	0.2	2	20	200	0	0.2	2	20	200
Aspartate aminotransferase activity	1.54	1.31	1.43	1.45	2.02	1.44	1.45	1.51	1.31	1.79

Leucine aminopeptidase activity	6.25	5.36	6.15	6.38	8.60	6.12	6.80	6.70	6.81	10.57
Alkaline phosphatase activity	0.94	1.20	1.07	1.20	1.92	0.94	0.93	1.07	1.26	1.49
Cholinesterase activity	0.46	0.43	0.45	0.42	0.45	1.20	1.03	1.25	1.17	0.59

At necropsy, organ weight was examined and revealed some changes. Lower brain, spleen, thymus and testes weights were observed at the highest dose level compared to the control group. Liver weight was increased at 200 mg/kg bw/d compared to the control group. Lung weight was not recorded. The microscopic examination revealed changes in heart (slight activation of the histiocytes), thyroid (single excretory ducts dilated and filled with granulocytes and cellular debris), lungs (massing clubbing of lymphocytes) and liver (nucleus anisomorphism, fatty degeneration and cell death).

Table 28 : Organ weight (in g and in %)

Dose level (in mg/kg bw/d)		Males					Females				
		0	0.2	2	20	200	0	0.2	2	20	200
Adrenal glands	Abs	0.063	0.071	0.072	0.072	0.065	0.066	0.068	0.075	0.069	0.068
	Rela	0.0179	0.0196	0.0205	0.0198	0.0271	0.0272	0.0281	0.0313	0.0294	0.0354
Brain	Abs	1.82	1.79	1.88	1.80	1.63	1.71	0.69	1.72	1.73	1.56
	Rela	0.516	0.495	0.537	0.496	0.673	0.704	0.703	0.720	0.735	0.822
Kidneys	Abs	2.80	2.91	2.93	2.93	2.48	1.97	2.06	2.04	1.86	2.14
	Rela	0.788	0.808	0.836	0.807	0.998	0.812	0.852	0.851	0.792	1.107
Liver	Abs	15.8	15.6	18.2	18.4	16.9	10.3	11.7	13.0	11.2	13.9
	Rela	4.43	4.31	5.19	5.02	6.76	4.23	4.79	5.42	4.74	7.22
Spleen	Abs	0.763	0.766	0.811	0.771	0.500	0.638	0.642	0.663	0.600	0.477
	Rela	0.215	0.212	0.231	0.212	0.198	0.262	0.264	0.276	0.254	0.248
Thymus	Abs	0.329	0.351	0.288	0.301	0.193	0.284	0.255	0.278	0.274	0.179
	Rela	0.093	0.097	0.082	0.081	0.070	0.117	0.105	0.115	0.117	0.093
Testes/ovary	Abs	3.03	3.07	3.04	3.13	2.17	0.106	0.108	0.106	0.121	0.097
	rela	0.84	0.85	0.86	0.86	0.86	0.0436	0.0444	0.0441	0.0514	0.0502

In a subchronic toxicity study (anonymous 24 (2000)), following OECD TG 408, 10 male and 10 female mice received 3-methylpyrazole via drinking water at a concentration of 0, 5, 10, 20 or 40 mg/kg bw/d during 13w. Additionally, 10 male and 10 female rats received 3-methylpyrazole, at the same concentration as the main groups, during 13w and were observed during 4w of recovery period.

No test article-related mortality or clinical signs were observed. Significant body weight changes were noted in males.

Table 29 : Body weight data (in g)

	Males	Females

Dose level (in mg/kg bw/d)	0	5	10	20	40	0	5	10	20	40
No. animals examined	20	20	20	20	20	20	20	20	20	20
D1	24.3	23.4*	24.1	23.4*	23.4*	20.3	20.0	20.1	20.0	20.4
D40	30.3	28.4**	28.9*	28.3**	27.9**	24.9	24.7	24.5	24.4	24.8
D89	33.3	30.2**	30.8**	30.5**	29.5**	26.7	26.1	26.9	26.4	26.5
Recovery groups										
No. animals examined	10	10	10	10	10	10	10	10	10	10
D5	32.9	29.8*	30.9	31.0	29.2**	26.1	26.8	26.5	26.4	26.7
D26	35.0	32.5	34.1	33.6	31.4*	27.2	27.2	27.4	27.4	27.6

* p < 0.05; ** : p < 0.01

Necropsy revealed few changes. Significant organ weight modifications were observed (see table 30). Lung weight was not recorded.

Table 30 : Organ weight (in g or %)

		Males					Females				
Dose level (in mg/kg bw/d)		0	5	10	20	40	0	5	10	20	40
After 13w											
FBW		30.0	25.4**	24.6**	24.9**	25.0**	26.1	25.6	25.4	24.6	25.1
Adrenal glands	Abs	0.008	0.007	0.008	0.007	0.008	0.014	0.015	0.012	0.014	0.015
	Rela	0.026	0.028	0.031	0.030	0.031	0.053	0.058	0.049	0.056	0.060
Brain	Abs	0.488	0.483	0.494	0.483	0.486	0.488	0.501	0.495	0.496	0.500
	Rela	1.643	1.912**	2.017**	1.969**	1.948**	1.872	1.964	1.965	2.018*	2.000
Liver	Abs	1.25	1.08	1.13	1.11	1.17	1.63	1.59	1.48	1.51	1.62
	Rela	4.15	4.27	4.59**	4.48	4.68**	6.23	6.22	5.85	6.14	6.48
Spleen	Abs	0.069	0.056	0.059	0.051**	0.065	0.082	0.084	0.083	0.083	0.081
	Rela	0.229	0.223	0.240	0.204	0.260	0.315	0.329	0.328	0.336	0.323
Testes	Abs	0.235	0.234	0.232	0.235	0.232					
	Rela	0.792	0.927**	0.947**	0.954**	0.928**					
Thymus	Abs	0.035	0.030	0.024**	0.025**	0.029	0.027	0.029	0.025	0.025	0.023
	Rela	0.117	0.116	0.099	0.100	0.115	0.104	0.114	0.098	0.100	0.091

* p < 0.05; ** : p < 0.01

The histopathology examination revealed changes in lungs such as an increase incidence of Clara cell alteration and proliferation.

Table 31 : Clara cells modifications

	Males					Females				
Dose level (in mg/kg bw/d)	0	5	10	20	40	0	5	10	20	40

After 13w											
Clara cell alteration	incidence	0	0	7	10	10	0	0	4	10	10
	Grade 1			3	2				1		
	Grade 2			4	7				2	6	
	Grade 3				1	5			1	4	3
	Grade 4					5					7
After 17w											
Clara cell alteration	Incidence	0	0	2	9	10	0	0	4	10	10
	Grade 1			1					1	1	
	Grade 2			1	7	1			3	9	
	Grade 3				2	9					10
Clara cell proliferation	Incidence	0	0	2	10	10	0	0	4	9	10
	Grade 1			2	2	3			3	2	1
	Grade 2				7	5			1	6	7
	Grade 3				1	2				1	2

A chronic toxicity study (anonymous 25 (1985)) exposed Wistar rats to 3-methylpyrazole during 18 months. Groups of 32 males and 32 females received the substance via drinking water at a concentration of 0, 10, 40 or 2000/1000 ppm. Due to the high mortality rate observed after 4 weeks (5 males and 8 females died), the highest dose level (2000 ppm) was reduced to 1000 ppm for the end of the exposure period (weeks 5 to 80).

Mortality was noted in control group and in all dose levels .

Table 32 : Mortality and body weight (in g) data

Dose level (in ppm)		0		10		40		40		2000/1000	
		Number of animals examined	bw	Number of animals examined	bw	Number of animals examined	bw	Number of animals examined	bw	Number of animals examined	bw
♂	W0	32	88	32	78	32	85	32	77	32	84
	W4	32	264	32	261	32	266	32	262	27	121
	W40	31	530	32	511	32	508	32	513	26	434
	W60	22	605	23	583	23	580	22	601	14	499
	W80	19	500	13	544	21	547	17	516	8	416
♀	W0	32	77	32	77	32	75	32	77	32	74
	W4	32	188	32	195	32	199	32	193	22	103
	W40	32	342	31	333	32	333	32	335	21	268
	W60	23	379	22	380	24	386	24	374	9	299
	W80	19	385	16	372	22	369	17	343	4	272

Dyspnea, cachexia and pneumonia were observed in all dose levels. At 2000/1000 ppm, body weight was reduced. Furthermore, hematology and bioclinical examination revealed changes at this dose level (see table 33).

Table 33 : Hematology and enzyme activity after 18 months

	Males	Females

Dose level (in ppm)	0	10	40	40	2000/1000	0	10	40	40	2000/1000
Hb	167.5	168.7	162.9	156.5	155.1	149.0	147.1	149.7	146.3	139.3
Ht	0.52	0.51	0.49	0.48	0.48	0.48	0.50	0.48	0.50	0.49
Alanine aminotrsanferase	1.29	1.16	1.29	1.19	1.24	1.11	1.18	1.43	0.98	1.77
Alkaline phosphatase	1.29	1.26	1.24	1.14	1.80	0.94	1.10	1.11	0.96	1.17
Aspartate aminotransferase	1.62	1.29	1.51	1.25	1.67	1.14	1.22	1.57	1.16	1.21
cholinesterase	0.48	0.51	0.50	0.53	0.47	1.71	1.54	1.34	1.61	0.83
Leucine aminopeptidase	5.52	4.79	5.37	3.94	5.92	5.67	6.29	6.17	5.34	8.43
Gamma globulin	13.56	13.10	12.05	11.57	10.87	11.79	13.11	12.17	11.95	10.03

Organ weight was examined and revealed few changes (see table 34). Lung weight was not recorded. The histopathological examination showed focal alteration in liver at 2000/1000 ppm.

Table 34 : Organ weight (in g or %)

		Males					Females				
Dose level (in ppm)		0	10	40	40	2000/1000	0	10	40	40	2000/1000
12 months											
Adrenal glands	Abs	0.064	0.063	0.060	0.056	0.052	0.083	0.084	0.093	0.091	0.083
	Rela	0.0110	0.0114	0.0110	0.0111	0.0115	0.0220	0.0246	0.0289	0.0236	0.0294
Brain	Abs	2.02	2.04	2.04	2.01	1.95	1.90	1.90	1.87	1.85	1.75
	Rela	0.350	0.368	0.375	0.399	0.432	0.512	0.557	0.581	0.480	0.629
Liver	Abs	23.8	24.1	19.5	17.1	21.8	13.3	15.4	13.1	13.8	15.8
	Rela	4.23	4.33	3.59	3.37	4.76	3.66	4.48	4.04	3.70	5.62
Spleen	Abs	0.825	0.907	0.801	0.805	0.779	0.690	0.747	0.621	0.665	0.544
	Rela	0.142	0.162	0.146	0.159	0.171	0.183	0.226	0.192	0.173	0.193
Thymus	Abs	0.162	0.169	0.139	0.152	0.137	0.138	0.109	0.126	0.107	0.126
	Rela	0.028	0.031	0.026	0.029	0.030	0.037	0.032	0.039	0.028	0.045
Testes ovary	Abs	3.86	3.89	3.93	3.87	3.67	0.102	0.102	0.118	0.097	0.082
	rela	0.67	0.70	0.72	0.76	0.81	0.0274	0.0302	0.0370	0.0253	0.0293
18 months											
Adrenal glands	Abs	0.084	0.068	0.071	0.100	0.057	0.098	0.113	0.094	0.110	0.070
	Rela	0.0192	0.0133	0.0140	0.0213	0.0146	0.0255	0.0325	0.0272	0.0331	0.0260
Brain	Abs	2.06	2.07	2.07	1.98	1.92	1.90	1.93	1.87	1.91	1.88
	Rela	0.459	0.399	0.396	0.412	0.474	0.504	0.563	0.538	0.578	0.704
Liver	Abs	22.5	22.9	21.7	20.3	20.0	16.0	15.5	16.4	14.5	13.8

	Rela	4.85	4.27	4.07	4.02	4.81	4.16	4.46	4.64	4.23	5.12
Spleen	Abs	0.866	0.788	0.975	0.767	0.794	0.715	0.790	0.701	0.695	0.609
	Rela	0.190	0.148	0.190	0.150	0.189	0.188	0.229	0.195	0.212	0.228
Thymus	Abs	0.121	0.103	0.131	0.139	0.105	0.085	0.095	0.073	0.106	0.131
	Rela	0.026	0.020	0.026	0.026	0.024	0.023	0.026	0.021	0.030	0.049
Testes ovary	Abs	3.46	3.79	3.95	3.65	3.25	0.107	0.107	0.100	0.112	0.090
	Rela	0.74	0.71	0.73	0.73	0.77	0.0280	0.0299	0.0291	0.0343	0.0333
Thyroid	Abs	0.046	0.041	0.044	0.075	0.048	0.038	0.042	0.036	0.050	0.049
	rela	0.0100	0.0077	0.0083	0.0159	0.0118	0.0100	0.0121	0.0102	0.0148	0.0183

Reproductive parameters were examined. In females, follicular maturation and evolution of corpus luteum were unaffected. Moreover, in males, no effects on spermiogenesis were observed.

Table 35: Extrapolation of equivalent effective dose for toxicity studies of greater or lesser duration than 90 days

Study reference	Effective dose (mg/kg/d)	Length of exposure	Extrapolated effective dose when extrapolated to 90-day exposure	Classification supported by the study
Short-term oral toxicity study in mice (anonymous 19 (1996))	135/173 mg/kg bw/d in males/females (alteration in lungs : Clara cell lesion and hypotrophy)	4w	45/57.6 mg/kg in males/females	STOT RE 1
Short-term oral toxicity study in mice (anonymous 20 (1997))	223/252 mg/kg bw/d (alteration in lungs : Clara cell alteration (moderate at the low and mid dose and marked at the high dose, haemorrhage, macrophages, ..)	4w	74.33/84 mg/kg bw/d	STOT RE 1

10.12.2 Comparison with the CLP criteria

Category 1	Category 2	Results available
"Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals , can be presumed to have the potential to produce significant toxicity in humans following repeated exposure. Substances are classified in category 1 for target organ toxicity (repeat exposure) on the basis of : - Reliable and good quality evidence from human cases or epidemiological studies; or - Observations from appropriate	"Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure. Substances are classified in category 2 for target organ toxicity (repeat exposure) on the basis of observations from appropriate studies in experimental animals which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations." Classification in Category 2 is applicable, when significant toxic effects observed in a 90-day repeated-dose study conducted in	In 2 short term oral toxicity studies (anonymous 19 (1996) and anonymous 20 (1997)), alteration in lungs were observed already at 135/173 and 223/252 mg/kg bw/d respectively in males/females of the 2 studies. The dose levels

studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations."

Classification in Category 1 is applicable, when significant toxic effects observed in a 90-day repeated-dose study conducted in experimental animals are seen to occur at or below the guidance values (C) as indicated in Table 3.9.2:

Table 3.9.2

Guidance values to assist in Category 1

Route of exposure	Units	Guidance values
Oral (rat)	Mg/kg bw/d	C≤10
Dermal (rat or rabbit)	Mg/kg bw/d	C≤20
Inhalation (rat) gas	ppV/6h/d	C≤50
Inhalation (rat) vapour	Mg/l/6h/d	C≤0.2
Inhalation (rat) dust/mist/fume	Mg/l/6h/d	C≤0.02

experimental animals are seen to occur within the guidance value ranges as indicated in Table 3.9.3:

Table 3.9.3

Guidance values to assist in Category 2 classification

Route of exposure	Units	Guidance values
Oral (rat)	Mg/kg bw/d	10<C≤100
Dermal (rat or rabbit)	Mg/kg bw/d	20<C≤200
Inhalation (rat) gas	ppV/6h/d	50<C≤250
Inhalation (rat) vapour	Mg/l/6h/d	0.2<C≤1.0
Inhalation (rat) dust/mist/fume	Mg/l/6h/d	0.02<C≤0.2

extrapolated to 90-day exposure (see table 35) were of 45/57.6 and 74.33/84 mg/kg bw/d. These effects were confirmed in the subchronic toxicity study. In the subchronic toxicity study (anonymous 24 (2000)), clara cell alteration were observed. These modifications was of grade 4 at the highest dose tested (40 mg/kg bw/d) and was always seen at the end of the recovery period. However these effects were not confirmed by clinical signs.

10.12.3 Conclusion on classification and labelling for STOT RE

Based on the effects observed in lungs (moderate to marked clara cell alteration), a classification as **STOT RE cat. 1 H372 Causes damage to organs (Lung)** is warranted.

10.13 Aspiration hazard

Not evaluated in this CLH dossier

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not evaluated in this CLH report.

12 ADDITIONAL LABELLING

NA

13 ABBREVIATIONS

* : p<0.05, statistically significant

** : p<0.01, statistically significant

♂ : male

♀ : female

↑ : increase

↓ : decrease

↓s : significantly decreased

Abs. : absolute

ADME : absorption, distribution, metabolism and excretion

ADE : absorption, distribution and excretion

ALP : alkaline phosphatase

ASAT : aspartate aminotransferase

BCOP : bovine corneal opacity/permeability test

Bw : body weight

Bwg : body weight gain

Cat. : category

chE : cholinesterase

Conc. : concentration

Corr. : corrosive

Dam. : damage

DMSO : dimethyl sulfoxide

Dpc : day post-coitum

E. Coli : Escherichia Coli

EC3 : estimated test substance concentration that will give a SI of 3

FBW : final body weight

GD : gestational day

GLP : good laboratory practive

Hb : haemoglobin

HPRT : hypoxanthine-guanine phosphoribosyl transferase

Ht : hematocrit

IVIS : *in vitro* irritancy score

LC50 : lethal concentration 50

LD50 : lethal dose 50

LLNA : local lymph node assay

M. : metabolism

Met. act. : metabolic activation

NA : not applicable

Nb.: number

NOAEL : no observed adverse effect level

OECD : Orgainisation for Economic Co-operation and development

PND : post natal day

Rela. : relative

S. Typh : Salmonella Typhimurium

SD : Sprague-Dawley

SI : simulation index

Sign. : significant

STOT RE : Specific target organ toxicity (repeated exposure)

STOT SE : Specific target organ toxicity (single exposure)

TG : test guideline

Tot. prot. : total protein

Tox. : toxicity

14 REFERENCES

Anonymous : see confidential annex chapter 15.2

Bleyl D.W.R (1990), 3-methylpyrazole-eine Modellsubstanz für Urogenitalschäden, Wiss. Z. Erns-Moritz. Arndt-Univ. Greifswald, 39(2), 21-22.

15 ANNEXES

- Confidential annex